

10/619,777

- 2 -

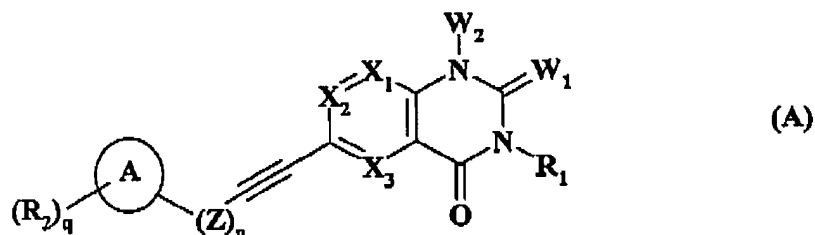
PC25131A

LISTING OF THE CLAIMS

The following listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of claims:

1 (currently amended). A combination, comprising valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13 of Formula (A)



or a pharmaceutically acceptable salt thereof, or an N-oxide thereof, wherein:

W_1 is O, S, or NR_3 , wherein R_3 is hydrogen, (C_1-C_6) alkyl, hydroxyl or cyano;

W_2 is selected from:

hydrogen;

trifluoromethyl;

NH_2 ;

(C_1-C_{10}) alkylN(H);

$[(C_1-C_{10})alkyl]_2N$, wherein each (C_1-C_{10}) alkyl moiety is the same or different;

(C_1-C_6) alkyl;

(C_3-C_6) alkenyl;

(C_3-C_6) alkynyl;

phenyl;

naphthyl;

phenyl- (C_1-C_{10}) alkyl;

naphthyl- (C_1-C_{10}) alkyl;

10/619,777

- 3 -

PC25131A

(C₃-C₁₀)cycloalkyl-(C₁-C₁₀)alkyl;

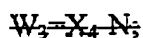
an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

a nonaromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 3 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

wherein in W₂ each (C₁-C₁₀)alkyl, (C₁-C₆)alkyl, (C₃-C₆)alkenyl, (C₃-C₆)alkynyl, phenyl, naphthyl, phenyl-(C₁-C₁₀)alkyl, naphthyl-(C₁-C₁₀)alkyl, (C₃-C₁₀)cycloalkyl-(C₁-C₁₀)alkyl, aromatic heterocycle, and nonaromatic heterocycle group is independently unsubstituted or substituted by from 1 to 3 groups, which may be identical or different, selected from halo, NH₂, (C₁-C₁₀)alkylN(H), [(C₁-C₁₀)alkyl]₂N, wherein each (C₁-C₁₀)alkyl moiety is the same or different, cyano, trihalo(C₁-C₆)alkyl, (C₁-C₆)acyl, C(=O)OR₄, -OR₄, and SR₄;

R₄ is hydrogen or (C₁-C₆)alkyl; or

~~W₂ and W₄ may be taken together to form a diradical group W₂-W₄ of formula~~



~~W₃ is N or CR₅ wherein R₅ is selected from:~~

~~hydrogen;~~

~~OR₆;~~

~~SR₆;~~

~~(C₁-C₆)alkyl;~~

~~(C₃-C₈)cycloalkyl;~~

~~a saturated heterocycle comprising from 3 to 8 ring members which are carbon atoms and one heteroatom selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;~~

~~phenyl;~~

~~naphthyl;~~

~~(C₅-C₁₀)heteroaryl comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;~~

~~phenyl-(C₁-C₁₀)alkyl; and~~

~~naphthyl-(C₁-C₁₀)alkyl;~~

10/619,777

- 4 -

PC25131A

~~R₆ is selected from hydrogen, (C₁-C₆)alkyl, phenyl (C₁-C₁₀)alkyl, and naphthyl (C₁-C₁₀)alkyl;~~

~~wherein in W₂ each (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, saturated heterocycle, phenyl, naphthyl, (C₅-C₁₀)heteroaryl, phenyl (C₁-C₁₀)alkyl, and naphthyl (C₁-C₁₀)alkyl group is independently unsubstituted or substituted by (CH₂)_p-OH or (CH₂)_p-NH₂;~~

~~p is an integer of from 0 to 4 inclusive;~~

~~X₄ is N or CR₇, wherein R₇ is selected from:~~

~~hydrogen;~~

~~NR₈R₉;~~

~~OR₈;~~

~~SR₈;~~

~~(C₁-C₆)alkyl;~~

~~(C₃-C₈)cycloalkyl;~~

~~a saturated heterocycle comprising from 3 to 8 ring members which are carbon atoms and one heteroatom selected from O, S, N(H), and N (C₁-C₁₀)alkyl;~~

~~phenyl;~~

~~naphthyl;~~

~~(C₅-C₁₀)heteroaryl comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N (C₁-C₁₀)alkyl;~~

~~phenyl (C₁-C₁₀)alkyl; and~~

~~naphthyl (C₁-C₁₀)alkyl;~~

~~R₈ and R₉ are the same or different, and are selected from hydrogen, (C₁-C₆)alkyl, phenyl (C₁-C₁₀)alkyl, and naphthyl (C₁-C₁₀)alkyl;~~

~~wherein in X₄ each (C₁-C₆)alkyl, (C₃-C₈)cycloalkyl, saturated heterocycle, phenyl, naphthyl, (C₅-C₁₀)heteroaryl, phenyl (C₁-C₁₀)alkyl, and naphthyl (C₁-C₁₀)alkyl group is independently unsubstituted or substituted by (CH₂)_p-OH or (CH₂)_p-NH₂, wherein p is an integer from 0 to 4 inclusive;~~

~~X₁, X₂ and X₃ independently of each other are N or C-R, One of X₁, X₂ and X₃ is N and the other two of X₁, X₂ and X₃ are C-R, wherein R is selected from:~~

~~hydrogen;~~

~~(C₁-C₆)alkyl;~~

10/619,777

- 5 -

PC25131A

hydroxyl;

(C₁-C₆)alkoxy;

halo;

trifluoromethyl;

cyano;

nitro;

S(O)_{n1}R₄, wherein R₄ is as defined above;NR₁₀R₁₁;n₁ is an integer of from 0 to 2 inclusive;R₁₀ and R₁₁ are the same or different, and are independently selected from

hydrogen;

(C₁-C₆)alkyl;phenyl-(C₁-C₁₀)alkyl; andnaphthyl-(C₁-C₁₀)alkyl; or

R₁₀ and R₁₁ may be taken together with the nitrogen atom to which they are bonded to form a 5-membered or 6-membered ring containing carbon atoms, the nitrogen atom to which R₁₀ and R₁₁ are attached, and optionally a second heteroatom selected from O, S, N(H), and N(C₁-C₁₀)alkyl,

~~wherein not more than two of the groups X₁, X₂, and X₃ simultaneously are a nitrogen atom;~~

n is an integer of from 0 to 8 inclusive;

Z is C(R₁₂)(R₁₃);Each R₁₂ and R₁₃ independently of each other are selected from:

hydrogen;

(C₁-C₆)alkyl;trihalo(C₁-C₆)alkyl;

halo;

NH₂;(C₁-C₆)alkylN(H);[(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety is the same or different;OR₄;

10/619,777

- 6 -

PC25131A

SR₄; and

C(=O)OR₄, wherein R₄ is as defined above; or

R₁₂ and R₁₃ on the same carbon atom may be taken together with the carbon atom to which they are attached to form a carbonyl group; and

Z can contain 1 carbon-carbon double bond when two R₁₂ groups are absent and n is an integer of from 2 to 8; and

Z can contain 2 carbon-carbon double bonds when four R₁₂ groups are absent or three R₁₂ and one R₁₃ groups are absent and n is an integer of from 3 to 8; and

Z can contain 1 carbon-carbon triple bond when two each of R₁₂ and R₁₃ are absent and n is an integer of from 2 to 8; and

Z can contain 2 carbon-carbon triple bonds when four each of R₁₂ and R₁₃ are absent and n is an integer of from 4 to 8; and

One C(R₁₂)(R₁₃) group in Z can be replaced with O, N(H), N(C₁-C₆)alkyl, S, S(O), or S(O)₂;

A is selected from:

phenyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

a nonaromatic 5-membered or 6-membered monocycle comprising carbon atoms and from 0 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

naphthyl;

an aromatic 8-membered to 12-membered bicycle comprising two aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 1 to 6 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

an aromatic 8-membered to 12-membered bicycle comprising one aromatic 5-membered or 6-membered ring and one non-aromatic 5-membered or 6-membered ring, wherein the rings may be bonded or fused to each other, and

10/619,777

- 7 -

PC25131A

wherein the bicycle comprises carbon atoms and from 0 to 6 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl; and
a non-aromatic 8-membered to 12-membered bicycle comprising two non-aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 4 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

Each R₂ may be the same or different, and is independently selected from:

hydrogen;
(C₁-C₆)alkyl;
halo;
cyano;
nitro;
trihalo(C₁-C₆)alkyl;
NR₁₀R₁₁;
OR₁₄;
SR₁₄;
S(O)R₁₄;
S(O)₂R₁₄;
(C₁-C₆)acyl;
(CH₂)_kNR₁₀R₁₁;
X₅(CH₂)_kNR₁₀R₁₁;
(CH₂)_kSO₂NR₁₄R₁₅;
X₅(CH₂)_kC(=O)OR₁₄;
(CH₂)_kC(=O)OR₁₄;
X₅(CH₂)_kC(=O)NR₁₄R₁₅;
(CH₂)_kC(=O)NR₁₄R₁₅; and
X₆-R₁₆;

X₅ is O, S, N(H), or N(C₁-C₆)alkyl;

k is an integer of from 0 and 3 inclusive;

R₁₀ and R₁₁ are as defined above;

10/619,777

- 8 -

PC25131A

R₁₄ and R₁₅ may be the same or different, and independently are hydrogen or (C₁-C₆)alkyl;

X₆ is a single bond, -CH₂-, O, or S, S(O), or S(O)₂;

R₁₆ is selected from:

phenyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

cyclopentyl;

cyclohexyl; and

a nonaromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 3 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

wherein in R₁₆ each phenyl, aromatic 5-membered or 6-membered, heterocyclic ring, cyclopentyl, cyclohexyl, and non-aromatic 5-membered or 6-membered heterocyclic ring group independently is unsubstituted or substituted with from 1 to 3 groups independently selected from (C₁-C₆)alkyl, halo, trihalo(C₁-C₆)alkyl, hydroxyl, (C₁-C₆)alkoxy, SH, (C₁-C₆)alkylthio, NH₂, (C₁-C₆)alkylN(H), [(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety may be the same or different;

q is an integer of from 0 to 7 inclusive;

R₁ is a group selected from:

hydrogen;

(C₁-C₆)alkyl;

(C₃-C₆)alkenyl; and

(C₃-C₆)alkynyl,

wherein in R₁ each (C₁-C₆)alkyl, (C₃-C₆)alkenyl, and

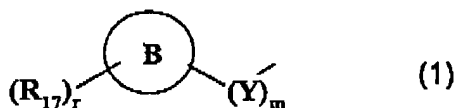
(C₃-C₆)alkynyl group is independently unsubstituted or substituted with from 1 to 3 groups independently selected from NH₂, (C₁-C₆)alkylN(H), [(C₁-C₆)alkyl]₂N,

wherein each (C₁-C₆)alkyl moiety may be the same or different, (C₁-C₆)alkyl, cyano, trihalo(C₁-C₆)alkyl, C(=O)OR₄, OR₄, SR₄, wherein R₄ is as defined above, and a group of formula (1)

10/619,777

- 9 -

PC25131A



m is an integer of from 0 to 8 inclusive,

Y is CR₁₈R₁₉;

Each R₁₈ and R₁₉ independently of each other, is selected from:

hydrogen;

(C₁-C₆)alkyl;

phenyl;

trihalo(C₁-C₆)alkyl;

halo;

NH₂;

(C₁-C₆)alkylN(H);

[(C₁-C₆)alkyl]₂N, wherein each (C₁-C₆)alkyl moiety may be the same or different;

OR₄;

SR₄; and

C(=O)OR₄;

R₄ is as defined above;

Y can contain 1 carbon-carbon double bond when two R₁₈ groups are absent and m is an integer of from 2 to 8; and

Y can contain 2 carbon-carbon double bonds when four R₁₈ groups are absent or three R₁₈ and one R₁₉ groups are absent and m is an integer of from 3 to 8; and

Y can contain 1 carbon-carbon triple bond when two each of R₁₈ and R₁₉ are absent and m is an integer of from 2 to 8; and

Y can contain 2 carbon-carbon triple bonds when four each of R₁₈ and R₁₉ are absent and m is an integer of from 4 to 8; and

One C(R₁₈)(R₁₉) group in Y can be replaced with O, N(H), N(C₁-C₆)alkyl, S, S(O), or S(O)₂;

B is a group selected from:

phenyl;

10/619,777

- 10 -

PC25131A

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

a nonaromatic 5-membered or 6-membered monocycle comprising carbon atoms and from 0 to 4 heteroatoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

naphthyl;

an aromatic 8-membered to 12-membered bicycle comprising two aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 1 to 6 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

an aromatic 8-membered to 12-membered bicycle comprising one aromatic 5-membered or 6-membered ring and one non-aromatic 5-membered or 6-membered ring, wherein the rings may be bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 6 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl; and

a non-aromatic 8-membered to 12-membered bicycle comprising two non-aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 4 hetero atoms selected from O, S, N(H), and N-(C₁-C₁₀)alkyl;

r is an integer of from 0 to 7 inclusive,

Each R₁₇ may be the same or different and independently is selected from:

hydrogen;

(C₁-C₆)alkyl;

halo;

cyano;

nitro;

tribalo(C₁-C₆)alkyl;

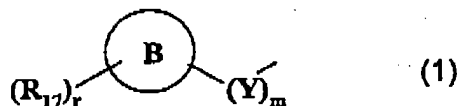
NR₁₀R₁₁;

OR₁₄;

10/619,777

- 11 -

PC25131A

 SR_{14} ; $S(O)R_{14}$; $S(O)_2R_{14}$; $(C_1-C_6)_{acyl}$; $(CH_2)_kNR_{10}R_{11}$; $X_5(CH_2)_kNR_{10}R_{11}$; $(CH_2)_kSO_2NR_{14}R_{15}$; $X_5(CH_2)_kC(=O)OR_{14}$; $(CH_2)_kC(=O)OR_{14}$; $X_5(CH_2)_kC(=O)NR_{14}R_{15}$; $(CH_2)_kC(=O)NR_{14}R_{15}$; and X_6-R_{16} , wherein X_5 , k , R_{10} , R_{11} , R_{14} , R_{15} , X_6 , and R_{16} are as defined above.**2 (original).** The combination of Claim 1, wherein: W_2 is $(C_1-C_6)_{alkyl}$; W_1 is O; and R_1 is a group of formula (1)wherein Y, B, R_{17} , m, and r are as defined for Formula (A) in Claim 1.**3 (original).** The combination of Claim 1, wherein the compound of Formula (A) is selected from:

4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid methyl ester;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid;

4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid;

4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid;

10/619,777

- 12 -

PC25131A

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;
4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;
4-benzyl-7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;
4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl}-benzoic acid methyl ester;
4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid; and
4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid;
or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

4 (original). The combination of Claim 1, wherein the compound of Formula (A) is selected from:

4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid methyl ester;
4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid;
4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl}-benzoic acid;
4-{6-[3-(4-methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid;
4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;
4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;
4-benzyl-7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;
4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl}-benzoic acid methyl ester;

10/619,777

- 13 -

PC25131A

4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid; and

4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid.

5 (currently amended). A pharmaceutical composition, comprising a combination of ~~valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkynyl inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof,~~ according to claim 1 and a pharmaceutically acceptable carrier, diluent, or excipient.

6 (currently amended). A method of treating a disease or disorder selected from cartilage damage, inflammation, arthritis, and pain in a mammal, comprising administering to the mammal a therapeutically effective amount of a combination of ~~valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkynyl inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof~~ according to claim 1.

7 (original). The method according to Claim 6, wherein the disease or disorder is rheumatoid arthritis.

8 (original). The method according to Claim 6, wherein the disease or disorder is osteoarthritis.

9 (original). The method according to Claim 6, wherein the disease or disorder is joint inflammation.

10 (original). The method according to Claim 6, wherein the pain is joint pain.